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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,399	DESJARLAIS ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,20,22-25,36,37 and 39-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20,22-25,36,37 and 39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 23 December 2008 has been entered.

Response to Amendment

Claims 17, 18, 22, 39-42 and 45 have been amended, and claims 26 and 38 have been canceled as requested in the amendment filed on 23 December 2008. Following the amendment, claims 17, 18, 20, 22-25, 36, 37 and 39-45 are pending in the instant application.

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are under examination in the instant office action.

Objections/Rejections Withdrawn

The objection to claims 17, 36 and 37 is withdrawn in response to the amendment to claim 17.

The rejection of claims 39-43 and 45 under 35 U.S.C. 112, second paragraph is withdrawn in response to the amendment to the claims to depend from claim 18.

The rejection of claims 17, 18, 20, 22-25, 36, 37 and 44 under 35 U.S.C. 102(b) as being anticipated by Loetscher et al. is withdrawn in view of the amendment to the claims, i.e. that the mixed TNFSF oligomer is substantially incapable of activating receptor signaling in all cognate receptors.

New issues are set forth below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 11/472,864. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '864 application are drawn to TNF-α variant proteins with amino acid substitutions

encompassed by the instant claims. Therefore, the instant claims and those of the '864 application are considered obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 6-11 of copending Application No. 11/559,379. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '379 application are drawn to compositions comprising TNF-α variant monomers and homotrimers with amino acid substitutions encompassed by the instant claims. Thus, the instant claims and those of the '379 application are considered obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

Claim Rejections - 35 USC § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 36, 37 and 45 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The claims are drawn to a mixed TNFSF oligomer and a pharmaceutical composition thereof comprising: a) one or two non-wild-type variant monomer(s) of a Tumor Necrosis Factor Super Family ("TNFSF") protein comprising at least a variant extracellular domain of said TNFSF monomer protein, wherein said variant TNFSF protein comprises an amino acid sequence that has at least one amino acid substitution in the Large Domain and at least one amino acid substitution in a domain selected from the group consisting of the DE Loop and the Small Domain; and, b) one or two wild-type TNFSF monomer(s) of said corresponding TNFSF protein; wherein said mixed TNFSF oligomer is substantially incapable of activating receptor signaling in all cognate receptors as compared to a homotrimer of said wild-type TNFSF oligomer.

The claims are not supported by either a substantial asserted utility or a well established utility because a variant TNFSF oligomer as claimed has no patentable real-world use. The instant disclosure is directed to variant TNF proteins that have the ability to form mixed trimers (oligomers) that have decreased receptor activity as compared to wild-type TNF proteins. Applicants teach that the monomer proteins are useful in treating disorders characterized by aberrant TNF activity. For example, the specification at p.2, paragraph [07], “A need still exists for proteins that can interfere

with intracellular signaling processes. Thus, it is an object of the present invention to provide proteins comprising multiple TNF superfamily receptor-interaction domains that are modified such that each domain has significantly reduced affinity and/or signaling capacity for the cognate receptor(s). Such linked domains preferably retain association with individual monomer domains, but exhibit a dominant-negative phenotype, antagonizing the action of related naturally occurring domains via their sequestration into inactive oligomeric complexes." (Emphasis added). Thus, "a variant TNF oligomer" is an inactive bi-product of using the variant TNF monomer proteins of the invention and has no real-world use.

Claims 17, 36, 37 and 45 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,672,347 to Aggarwal et al. (issued 30 September 1997), in view of Loetscher et al. (cited previously).

The Aggarwal patent discloses methods of treating autoimmune or inflammatory disorders (which are TNFSF meditated diseases) comprising administration of therapeutically effective amounts of an antagonist for TNF and teaches pharmaceutical compositions thereof, as in claim 45. The patent describes the function of the antagonists as either binding to or sequestering the TNF molecule itself with sufficient

affinity and specificity to substantially neutralize the TNF epitopes responsible for TNF receptor binding or to compete with native TNF for the cell surface receptor or intracellular site to which TNF binds in the course of cell lysis (col.4, lines 48-65). Examples include TNF antagonistic variants, which include substitutions, deletions or insertions of residues (amino acid sequence variants). Antagonistic TNF amino acid sequence variants are described as variants of the mature TNF amino acid sequence that are capable of inhibiting TNF cytotoxic activity, but which have substantially no cytotoxic activity of their own (col.5, lines 7-23). The difference between the disclosure of the Aggarwal patent and the claimed invention is that the patent does not teach the specific TNF substitutional variants of the instant claims.

However, upon reading the disclosure of the Aggarwal patent, the skilled artisan would have recognized the desirability of developing improved TNF substitutional variants for the treatment of TNF mediated diseases, i.e. autoimmune disorders or inflammatory disorders. Furthermore, Loetscher teaches mutated human TNF monomer proteins, which were analyzed for selective binding to recombinant p55 and p75 TNF receptors in competition with radiolabeled wild-type TNF. The reference teaches that mutations in the loop from position 29 to 34 (as in claim 43) and at positions 86 and 146 preferentially impaired binding to the 75-kDa TNF receptor, whereas mutations in the region from 143 to 145 mainly affected binding to the 55-kDa TNF receptor (abstract). The reference teaches mutants with substitutions at residues 65-76 (p.26352, col.2, third paragraph under Results), as in claim 40. The reference teaches that the substitutions are at receptor contact positions (p.26351, col.1), as in claim 23, and

teaches surface substitutions (p.26352, col.1, first paragraph under Results), as in claim 37. In addition, the reference teaches non-conservative substitutions (e.g., p.26353, Table 1), as in claim 36. The reference teaches that selectivity for one or the other receptor type was enhanced by combining two or three point mutations, the effects of the single mutations with respect to receptor selectivity being at least additive (abstract). Loetscher teaches that the mutants assembled into trimers, i.e. oligomers (p.26352, col.2, fourth paragraph under Results). The reference teaches that mutation of the conserved tyrosine 87 (Y87) amino acid residue resulted in a dramatic loss of binding activity to both TNF receptors (abstract, p.26352, second paragraph under Results, Table III on p.26355 and paragraph spanning pp.26355-26356). Mutants comprising the mutation A145R exhibited a complete loss of binding to the p55 TNF receptor and a 5-10 fold decrease in binding to the p75 TNF receptor and demonstrated no cytotoxic effects in a TNF cell cytotoxicity assay, even when present at high concentrations (p.26356, col.2, second paragraph). Loetscher does not explicitly disclose a TNF variant protein or mixes oligomer thereof that is substantially incapable of activation receptor signaling in all cognate receptors (both p55 and p75 receptors), with at least one substitution in the Large domain and at least one substitution in either the DE loop or the Small domain, as claimed.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the compositions and methods of Aggarwal as taught by Loetscher to yield predictable results. As evidenced by the Aggarwal patent, the skilled artisan would have known that developing TNF variant antagonists for

methods of treating TNFSF mediated diseases, i.e. inflammatory or autoimmune disorders, would be desirable. The patent specifically guides the artisan to treat with TNF substitutional variants that are antagonistic to TNF receptors and are capable of inhibiting TNF cytotoxic activity, but which have substantially no cytotoxic activity of their own. As evidenced by the Loetscher reference, the skilled artisan would have known that TNF substitutional variants comprising mutations at tyrosine 87 are not capable of binding to both TNF receptors and that mutants comprising the substitution A145R exhibit decreased binding to both receptors and exhibit no cytotoxicity (and would thus be useful as antagonists described by Aggarwal). A TNF variant monomer comprising both of these substitutions would meet all of the limitations of claims 17, 18, 20, 22-25, 36, 37, 39, 41, 42 and 44. As evidenced by both references, administration of the TNF variant monomer proteins for treatment of TNF-related disease would result in the formation of TNF mixed oligomers that are inactive bi-products of the treatment methods. Thus, it would have been reasonable to predict that the treatment methods of Aggarwal could be successfully practiced with TNF antagonistic protein variants that comprise substitutions taught by Loetscher. Given that Loetscher et al. teach the effect of combining single mutations would be additive and teach substitutions at positions that would abolish binding to either or both cognate receptors, which would be desirable for Aggarwal's methods, the skilled artisan would have found it obvious to generate a TNF mutant comprising the claimed substations for use in Aggarwal's methods. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. If this leads to the anticipated success, it is

likely the product not of innovation but of ordinary skill and common sense. The motivation to arrive at the claimed invention flows naturally from the disclosure of the prior art references.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
12 April 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
4/13/2009